a1

- enzymatic conversion of HPP into HPA with a first suitable enzyme, then
- enzymatic conversion of HPA into HMO with a second suitable enzyme.

a2

11. (amended) Method according to one of Claims 1 to 8, characterized in that it is carried out in the presence of an HPPD inhibitor.

REMARKS

The Office Action of October 26, 2002 has been carefully considered and this response prepared. Claims 1-11 are pending in the application. Claims 9 and 10 have been canceled without prejudice. Claims 1 and 11 have been amended. Claim 1 has been amended to state that the method is carried out in a plant cell modified to produce a first suitable enzyme that converts 4-hydroxyphenyl pyruvate (HPP) to 4-hydroxy-phenylacetate (HPA) and a second suitable enzyme that converts HPA into homogentisate (HMO). Support for this amendment can be found in the specification at page 4, lines 9-19. The dependency of claim 11 has been amended.

At page 3 of the Office Action, the Examiner rejected claims 1-3, 5-7 and 9-10 under 35 USC 102(b) as being anticipated by Suemori *et al.*, Semei Kogaku Kogyu Gijutsu Kenkyusho Kenkyu Hohoku 3(2): 33-36, (1995). The Examiner indicated that this reference discloses the enzymatic bioconversion of 4-hydroxyphenylpyruvate (HPP) into 4-hydroxyphenylacetate (HPA) and the enzymatic bioconversion of HPA into homogentisate (HMO), using *Rhodococcus erythropolis* and also discloses the use by this strain of HPP or HPA as the sole carbon source.

Applicants traverse this rejection. Suemori *et al.* discloses experiments on the degradation of phenylalanine and tyrosine in the gram-positive bacterium *R. erythropolis*. The authors concluded that tyrosine was degraded through HPP and HPA to HMO.

Claims 1-8 and 11, as amended, are not anticipated by Suemori *et al.* The method of claims 1-8 and 11 is carried out in a transformed plant cell which is not disclosed by Suemori *et al.* Withdrawal of this section 102(b) rejection is requested.

Also at page 3 of the Office Action, the Examiner rejected claims 1-11 under 35 USC 103(a) as being *prima facie* obvious over Suemori *et al.* (1995) taken with Suemori *et al.*, Journal of Fermentation and Bioengineering 81: 133-137, 1996; Hareland *et al.*, J. Bacteriology 121: 272-285, 1975 and Blakley *et al.* Canadian Journal of Microbiology 23: 1128-1139, 1977. The basis for this rejection is that it would have been obvious to one skilled in the art to modify the process of Suemori *et al.* by using further enzymes from other microorganisms for the enzymatic bioconversion of HPP into HPA and the enzymatic bioconversion of HPA into HMO for the expected benefits of maximizing the yield of this valuable compound useful in a variety of pharmaceutical and industrial applications.

Applicants traverse this rejection.

Suemori *et al.* (1995) has been discussed above.

Suemori *et al.* (1996) discloses purification and characterization of three monohydroxyphenylacetate monooxygenases, o-hydroxyphenylacetate 5-hydroxylase, m-hydroxyphenylacetate 6-hydroxylase and p-hydroxyphenylacetate 1-hydroxylase from the bacterium *Rhodococcus erythropolis*. The authors found that p-hydroxyphenylacetate 1-hydroxylase converted p-hydroxyphenylacetate to HMO.

Blakley *et al.* discloses experiments on the degradation of tyrosine by an *Arthrobacter* species. In this microorganism, the authors found that HPP was formed from tyrosine by an aminotransferase. The HPP was then converted to HPA by p-hydroxyphenylpyruvate oxidase. HPA was then converted to 3, 4-dihydroxyphenyl acetate by a p-hydroxyphenylacetate hydroxylase that appeared to have properties similar to p-hydroxyphenylacetate 3-hydroxylase.

Hareland *et al.* discloses studies of the metabolic function and properties of 4-hydroxyphenylacetic acid 1-hydroxylase from *Pseudomonas acidovarans*.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or

motivation in the prior art to do so. The mere fact that the prior art may be modified to reflect features of the claimed invention does not make modification, and hence the claimed invention, obvious unless the desirability of such modification is suggested by the prior art.

Suemori *et al.* (1995) discloses studies on the degradation of tyrosine in *R. erythropolis* where the authors concluded that tyrosine was degraded through HPP and HPA to HMO. Suemori *et al.* makes no suggestion whatever about the possibility or desirability of substituting enzymes from other microorganisms for the ones in *R. erythropolis* to produce HMO.

Suemori *et al.* (1996), Hareland *et al.* and Blakley *et al.* do not supply what is missing from Suemori *et al.*

Suemori *et al.* (1996) discloses purification and characterization of a HPA hydroxylase from the bacterium *R. erythropolis*, which is the same bacterium used by Suemori *et al.* (1995) and is hence not from a different microorganism. Moreover, there is no suggestion in Suemori *et al.* (1996) of combining enzymes from other microorganisms to produce HMA.

Hareland *et al* and Blakley *et al.* each disclose one of the enzymes that are useful in Applicants' claimed method, HPA hydroxylase and HPP oxidase, respectively. Neither of these references makes any suggestion whatever about the possibility or desirability of substituting enzymes from other microorganisms to produce HMO.

The combination of Suemori *et al.* (1995) with Suemori *et al.* (1996), Hareland *et al.* and Blakley *et al.* amounts to an impermissible hindsight reconstruction of the claimed invention from isolated disclosures in the prior art. There is nothing in the cited references, alone or in combination, that suggest Applicants' claimed method of producing HMA by enzymatic means.

Even assuming *arguendo* that the references were properly combined, there is nothing in the combined teachings of the cited references that suggests the possibility or desirability of combining the enzymes from various microorganisms to produce HMO.

Before the disclosures of two or more prior art references can be combined in order to establish *prima facie* obviousness, there must be some suggestion or motivation

in the prior art for making the combination. In the present rejection, *prima facie* obviousness has not been established. There is no suggestion in any of the references, alone or in combination, supporting the Examiner's assertions that it would have been obvious to modify the process of Suemori *et al.* (1995) by using enzymes from other microorganisms to produce HMO.

Claims 1-8 and 11, as amended, are drawn to a method for enzymatic preparation of HMO from HPP wherein the method is carried out in a plant cell modified to produce a first suitable enzyme that converts HPP to 4-hydroxyphenylacetate (HPA) and a second suitable enzyme that converts HPA into HMO. None of the cited references, alone or in combination, discloses or suggests carrying out synthesis of HMO in such a modified plant cell. Each of the cited references discloses experiments with bacteria. Plants cells are not disclosed.

Claims 1-8 and 11 are not obvious over Suemori *et al.*(1995) in view of Suemori *et al.* (1996), Hareland *et al.* and Blakley *et al.* Withdrawal of this section 103(a) rejection is requested.

In view of the above, the present application is believed to be in a condition for allowance. Reconsideration of the application is requested and an early Notice of Allowance is earnestly solicited.

Respectfully submitted,
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Appendix A

Marked up amended claims

1. (amended) Method for enzymatic preparation of homogentisate (HMO) from 4-hydroxypyruvate (HPP), characterized in that it consists in carrying out <u>in a plant cell modified to produce a first suitable enzyme that converts HPP to 4-hydroxyphenylacetate (HPA) and a second suitable enzyme that converts HPA into HMO</u>, [in a suitable reaction medium,] the following enzymatic reactions:

- enzymatic conversion of HPP into [4-hydroxyphenylacetate] HPA with a first suitable enzyme, then
- enzymatic conversion of HPA into HMO with a second suitable enzyme.

11. (amended) Method according to one of Claims [1 to 10] <u>1 to 8</u>, characterized in that it is carried out in the presence of an HPPD inhibitor [in the suitable reaction medium].